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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/384,248	02/06/95	ALIZON	M 3495.0008-08

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PARKIN, J EXAMINER	
ART UNIT	PAPER NUMBER
1813	

DATE MAILED:
08/20/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/384,248	Applicant(s) Alizon et al.
	Examiner Jeffrey S. Parkin, Ph.D.	Group Art Unit 1813

Responsive to communication(s) filed on 5/22/96

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 23, 32, and 33 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 23, 32, and 33 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Response to Paper

1. Acknowledgement is hereby made of the RESPONSE TO PAPER No. 16. Claims 23, 32, and 33 are currently under examination.
2. The text of those sections of Title 35, U.S. Code not included in 5 this action can be found in a prior Office action.
3. Applicants requested clarification concerning the nature of the previous rejection of claims 23, 32, and 33 under 35 U.S.C. 112, first paragraph. These claims are rejected under this section 10 because the instantly claimed subject matter is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Accordingly, the specification fails to provide an adequate written description of the 15 invention as presently filed. Applicants are reminded that the instantly claimed invention is directed towards antibody production methods employing HIV-1 antigens, the generation of antibodies against said antigens, and the recovery of said antibodies. This rejection is based upon the inability of the specification to provide 20 demonstrative evidence that applicants were in possession of the claimed HIV-1 antigens (i.e. the Gag, Pol, and Env proteins purportedly encoded by the λ-J19 inserts) and that methods for the production and recovery of HIV-1 specific antibodies were adequately described.

Applicants' traversal, as it applies to the aforementioned rejection, can be summarized as follows:

- (1) Applicants need not describe each and every embodiment of the claimed invention;
- 5 (2) The Office must supply evidence suggesting that the invention is nonenabled to establish a *prima facie* case for lack of enablement;
- (3) Applicants argue that the precise coding regions of the λ -J19 inserts need not be disclosed, since the skilled artisan could readily ascertain this information;
- 10 (4) Applicants argue that "theoretical caveats" do not provide a *prima facie* basis for lack of enablement; and,
- (5) The Office can not rely upon the "persuasive representation" of the background information of a U.S. patent.

Applicants' arguments have been thoroughly considered but are deemed 15 to be nonpersuasive as elaborated below.

The outstanding rejection is based upon the inability of the applicants to provide definitive support that they were in possession of the instantly claimed HIV-1 antigens and contemplated employing said antigens in the generation and isolation of HIV-1-specific 20 antisera. As previously disclosed the specification is clearly directed towards HIV-1 nucleic acids and molecular clones. Specifically, the specification teaches the isolation of a novel viral genomic clone, λ -J19, obtained from LAV-infected T-lymphocytes. Said clone was obtained by screening a genomic library with an LAV 25 LTR cDNA probe. Preliminary restriction analysis was performed and

a tentative restriction map obtained (refer to Figure 2). Perusal of the specification indicates that the instantly claimed methods of producing antibodies to HIV-1 antigens are clearly not enabled. The specification is clearly directed towards the production of HIV-1_{Bru} 5 CDNA fragments and the utilization of said probes in diagnostic assays to detect LAV DNA or RNA. Specifically, the applicants state (refer to page 1 of the specification) that "The invention relates to cloned DNA sequences hybridizable to genomic RNA and DNA of lymphadenopathy-associated virus (LAV), a process for their preparation and their uses. It relates more particularly to stable probes including a DNA sequence which can be used for the detection of the LAV virus or related viruses or DNA proviruses in any medium, particularly biological samples containing any of them."

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Applicants argue that ample support for the invention is provided 15 on pages 13 and 14 of the specification. These pages only provide a suggestion that the isolated LAV nucleic acids may be suitable for the expression of viral antigens. Specifically, the specification states (page 13, lines 12-15) that "The DNA according to the invention can be used also for achieving the expression of LAV viral 20 antigens for diagnostic purposes as well as for the production of a vaccine against LAV." This portion of the specification does not provide adequate written support for the instantly claimed invention, which is directed towards prepared HIV-1 antigens, methods of generating specific antibodies, and methods for the recovery of said 25 antibodies. Applicants are invited to identify those portions of the

specification that provide direct support for the preparation of HIV-1 viral antigens and antibodies.

The arguments presented in the last Office action illustrate a number of pragmatic concerns, not "theoretical" constraints, directed 5 towards the expression and purification of viral antigens. To express a known viral antigen, one practicing the invention needs to know the precise coding region of any particular DNA fragment. However, as previously disclosed the specification does not provide any demonstrable evidence suggesting that the instantly claimed 10 restriction fragments are capable of encoding the claimed viral antigens. Applicants are reminded that the instantly claimed restriction fragments are "thought to correspond at least in part to the gene coding for the envelope", "thought to correspond at least in part to the pol gene", and "thought to correspond at least in part to the gag gene" (refer to the specification, pages 4 and 5). However, 15 the ability of these restriction fragments to actually encode the recited HIV-1 antigens is not taught nor is it reasonably suggested by the prior art. The specification fails to provide any nucleotide sequence data pertaining to the aforementioned restriction fragments, 20 which precisely identifies the initiation and termination codons of any of the recited antigens. Moreover, applicants readily admit in the specification that it is not readily manifest that these restriction fragments are actually capable of encoding the specified antigens. How could the applicants be in possession of the instantly 25 claimed invention (i.e. HIV-1 antigens) when the specification

clearly indicates that the coding potential of these fragments is unknown?

Moreover, it was previously emphasized that the HIV/SIVs display considerable genomic heterogeneity and exist as a quasispecies
5 (Goodenow et al., 1989, J. Acquir. Immun. Defic. Syndr. 2:344-352). Each viral strain contains peptides with independent and distinct amino acid sequences, biochemical, and immunologic properties. Goodenow and colleagues examined genetic variation in HIV-1 and concluded on page 351 that "we are faced by a virus of enormous
10 complexity, certainly more heterogeneous than influenza A or poliovirus (24). The data described here suggest that there may be as many viral strains of HIV-1 as there are carriers...The possibility of viral mixtures within isolates as well as the high frequency of apparently defective genomes render the task of the
15 molecular biologist difficult." The prior art clearly illustrates the problems associated with obtaining HIV-1 molecular clones that encode for the desired antigens. These are not "theoretical" concerns, but have been well documented experimentally. However, it is the applicants contention that their existing restriction
20 fragments, of unknown sequence and coding potential, indicate that they were clearly in possession of the instantly claimed HIV-1 viral antigens. This assertion contradicts the teachings of the art and would be readily questioned by the skilled artisan.

Additional references were provided to emphasize that even if the
25 restriction fragments were capable of encoding for viral antigens,

which clearly has not been established, the expression and purification of viral antigens is often problematic (Kamtekar et al., 1993, Science 262:1680-1685). The authors succinctly described the caveats associated with protein expression and purification as 5 follows:

Because each of our synthetic genes has a different DNA sequence (19), each clone has the potential to express a different protein sequence. However, cloning a designed DNA sequence does not ensure expression of a protein that is compact, soluble, and resistant to intracellular proteases. Overexpression of many natural proteins has been hindered by difficulties with folding, stability, or solubility (20). In attempting to express a de novo designed sequence, three possible outcomes must be 10 15 considered:

1) No expression is observed. If the designed sequence does not fold into a stable compact structure then it will be proteolyzed in vivo and will fail to accumulate in the cell (21). It is also possible that some proteins fail to 20 be expressed because transcription or translation rates are diminished by particular RNA structures or codon usage patterns.

2) Expression is observed, but the protein forms 25 insoluble inclusion bodies. Insoluble aggregates of misfolded chains are frequently observed when natural proteins are expressed in large amounts (20, 22). Although the polypeptide chains sequestered in inclusion bodies are resistant to intracellular proteolysis, no conclusions can be drawn about their folded structures.

3) Expression of soluble protein is observed. The 30 accumulation of a soluble protein requires that it escape degradation by cellular proteases. The ability of a soluble protein to resist proteolysis is far greater if it folds into a compact and stable structure than if it exists as an unfolded polypeptide chain (21). Thus, the ability 35 of a novel protein to withstand proteolysis in vivo is evidence for the formation of a compact structure.

Accordingly, the successful expression of recombinant cellular and 40 viral proteins is contingent upon a number of complex and contributory factors. Once again, these are not merely "theoretical" concerns, but are based upon appropriate biochemical experimentation.

The rejection of claims 23, 32, and 33 under 35 U.S.C. § 112, first paragraph, is hereby maintained for the reasons set forth in the objection to the specification. Applicants may obviate this rejection by providing appropriate scientific documentation 5 addressing the aforementioned concerns.

4. Claim 23 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Putney et al. (1986). Applicants traverse and note that this application claims priority to U.S. application serial no. 10 06/771,230, filed August 30, 1986. However, as disclosed *supra* the instantly claimed invention is not enabled and has not been extended the benefit of this priority date. Accordingly, this rejection is hereby maintained.

15 5. Claims 23, 32, and 33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Luciw and Dina (1992, US PAT 5,156,949). Applicants traverse and note that this application claims foreign priority to GB 84/23659, filed September 19, 1984 and domestic priority to U.S. application serial no. 06/771,230, filed August 30, 20 1986. However, as disclosed *supra* the instantly claimed invention is not enabled and has not been extended the benefit of these priority dates. Accordingly, this rejection is hereby maintained.

25 6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

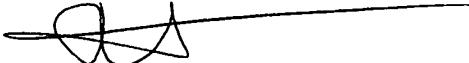
5 A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS
SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE
EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE
OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL
10 AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE
SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY
ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R.
S 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY
ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE
15 LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

20 7. Correspondence related to this application may be submitted to
15 Group 1813 by facsimile transmission. The faxing of such papers must
conform with the notice published in the Official Gazette, 1096 OG 30
(November 15, 1989). The fax number for Group 1813 is **(703) 305-7939**.
Applicants are encouraged to notify the Examiner prior to the
substitution of such documents to facilitate their expeditious
processing and entry.

25 8. Any inquiry concerning this communication should be directed to
Jeffrey S. Parkin, Ph.D. whose telephone number is **(703) 308-2227**.
The examiner can normally be reached Monday through Friday from 8:30
AM to 6:00 PM. A message may be left on the examiner's voice mail
service. If attempts to reach the examiner are unsuccessful, the
examiner's supervisor, **Ms. Christine Nucker** can be reached at **(703)**
308-4028. Any inquiry of a general nature or relating to the status
30 of this application should be directed to the Group 1813 receptionist
whose telephone number is (703) 308-0196.

Respectfully,

35


Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1813

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August 15, 1996



CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180